Lung Function Growth in Children with Long-Term Exposure to Air Pollutants in Mexico City

Rosalba Rojas-Martinez[1], Rogelio Perez-Padilla[2], Gustavo Olaiz-Fernandez[1], Laura Mendoza-Alvarado[1], Hortensia Moreno-Macias[1,3], Teresa Fortoul[4], William McDonnell[5], Dana Loomis[5], and Isabelle Romieu[1]

[1]Instituto Nacional de Salud Publica, Cuernavaca, Mexico; [2]Instituto Nacional de Enfermedades Respiratorias, Mexico City, Mexico; [3]Universidad Autónoma Metropolitana, Mexico City, Mexico; [4]Medical School, UNAM, Mexico City, Mexico; and [5]School of Public Health, University of North Carolina, Chapel Hill, North Carolina

***Rationale*: Although short-term exposure to air pollution has been associated with acute, reversible lung function decrements, the impact of long-term exposure has not been well established.**

***Objectives*: To evaluate the association between long-term exposure to ozone (O_3), particulate matter less than 10 μm in diameter (PM_{10}), and nitrogen dioxide (NO_2) and lung function growth in Mexico City schoolchildren.**

***Methods*: A dynamic cohort of 3,170 children aged 8 years at baseline was followed from April 23, 1996, through May 19, 1999. The children attended 39 randomly selected elementary schools located near 10 air quality monitoring stations and were visited every 6 months. Statistical analyses were performed using general linear mixed models.**

***Measurements and Main Results*: After adjusting for acute exposure and other potential confounding factors, deficits in FVC and FEV_1 growth over the 3-year follow-up period were significantly associated with exposure to O_3, PM_{10}, and NO_2. In multipollutant models, an interquartile range (IQR) increase in mean O_3 concentration (IQR, 11.3 ppb) was associated with an annual deficit in FEV_1 of 12 ml in girls and 4 ml in boys, an IQR range (IQR, 36.4 $\mu g/m^3$) increase in PM_{10} with an annual deficit in FEV_1 of 11 ml in girls and 15 ml in boys, and an IQR range (IQR, 12.0 ppb) increase in NO_2 with an annual deficit in FEV_1 of 30 ml in girls and 25 ml in boys.**

***Conclusions*: We conclude that long-term exposure to O_3, PM_{10}, and NO_2 is associated with a deficit in FVC and FEV_1 growth among schoolchildren living in Mexico City.**

Keywords: lung function growth; air pollution; children

Epidemiologic studies have shown that acute exposure to ambient air pollution is associated with a range of respiratory events in children (1–3). Although there is growing evidence that air pollution exposure is likely to affect lung growth (4–10), there is controversy on which pollutant is most harmful to health. Long-term exposure to ozone (O_3) has been associated with significantly decreased lung function in retrospective and prospective cohorts of children (6, 11) and young adults (4, 5), and the Children's Health Study (CHS) (7–9) has reported that nitrogen dioxide (NO_2), acid vapor, and elemental carbon had the strongest effect.

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Epidemiologic studies addressing the effects of long-term exposure to air pollutants on lung function growth in children are not conclusive.

What This Study Adds to the Field

Long-term exposure to air pollutants is associated with a significant deficit in lung function growth in children.

The metropolitan area of Mexico City experiences significant air pollution problems. O_3 levels are high, and the average 1-hour daily maximum frequently exceeds 110 ppb (the Mexican standard) (12). Studies conducted among children with asthma who live in Mexico City have shown a decrement in lung functions and an increase in respiratory symptoms (13–16), suggesting that children with lifelong exposure to a heavily polluted environment, mainly to ozone pollution, have detectable abnormalities that could be indicative of small airway disease or decreased total lung capacity.

We conducted a prospective dynamic cohort study to evaluate the long-term effect of ambient air pollution on the lung function growth of Mexico City schoolchildren. Some of the results of this study have been previously reported in the form of abstracts (17, 18).

METHODS

Study Design

We selected 10 fixed-site air monitoring stations in Mexico City and randomly selected 39 elementary schools from among those located within 2 km of the stations. The study cohort consisted of students of the selected schools who were 8 years of age at the beginning of the study, who had not been diagnosed as having asthma, and whose parents had signed a consent letter. A substantial number of children entered or left the cohort during the course of the study. At baseline, a questionnaire was completed by the parents of 1,819 children, and a spirometric test was administered to each child (phase 1). An additional 1,351 participants of the same age ($\pm$1 mo) as the previously enrolled children were added to the cohort in subsequent phases. The cohort was followed every 6 months (spring and fall) for 3 years with spirometric tests and two questionnaires, one completed by the parents and the other by the children and their teachers. Lung function testing was conducted by trained technicians following American Thoracic Society standards (19), using computerized dry rolling-seal spirometers (model 922; SensorMedics, Yorba Linda, CA). The spirometry quality control program has been previously reported (20).

(*Received in original form October 27, 2005; accepted in final form April 19, 2007*)

Supported by the Mexican Sciences and Technology Council (CONACYT), SALUD-2005-01-13956 and by the National Center for Environmental Health–Centers for Disease Control and Prevention, Atlanta, GA.

Correspondence and requests for reprints should be addressed to Isabelle Romieu, M.D., M.P.H., Sc.D., Instituto Nacional de Salud Publica, 655 Avenida Universidad, Col. Santa Maria Ahuacatitlán, Cuernavaca, Morelos 62508, México. E-mail: iromieu@correo.insp.mx

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 176. pp 377–384, 2007
Originally Published in Press as DOI: 10.1164/rccm.200510-1678OC on April 19, 2007
Internet address: www.atsjournals.org

TABLE 1. STUDY POPULATION CHARACTERISTICS BY STUDY PHASE AND SEX, MEXICO CITY, 1996–1999

	Study Phase						
Variable	1 Spring 1996	2 Fall 1996	3 Spring 1997	4 Fall 1997	5 Spring 1998	6 Fall 1998	7 Spring 1999
Total, n	1,819	1,906	2,321	2,204	1,859	2,218	2,218
Girls, n	929	944	1,161	1,117	942	1,113	1,115
Age, yr	8.7	9.1	9.6	10.2	10.6	11.1	11.6
Weight, kg	29.7	31.3	34.6	37.4	39.8	42.8	45.0
Height, cm	130.6	133.3	137.3	140.5	143.4	146.3	149.1
BMI	17.2	17.5	18.2	18.7	19.2	19.9	20.1
FVC, L	2.0	2.1	2.2	2.4	2.5	2.8	2.9
FEV_1, L	1.7	1.8	2.0	2.1	2.2	2.5	2.6
$FEF_{25–75\%}$, L/s	2.2	2.4	2.7	2.9	3.1	3.4	3.5
Boys, n	890	962	1,160	1,087	917	1,105	1,103
Age, yr	8.7	9.2	9.7	10.2	10.7	11.2	11.7
Weight, kg	30.0	32.1	34.6	37.5	39.6	41.8	44.3
Height, cm	131.0	133.7	136.8	139.8	142.8	145.5	148.7
BMI	17.4	17.8	18.3	19.0	19.2	19.6	19.8
FVC, L	2.2	2.3	2.4	2.5	2.6	2.9	3.1
FEV_1, L	1.9	2.0	2.1	2.2	2.3	2.5	2.7
$FEF_{25–75\%}$, L/s	2.2	2.5	2.6	2.7	2.8	3.1	3.2

Definitions of abbreviations: BMI = body mass index; $FEF_{25–75}$ = forced expiratory flow, midexpiratory phase.

TABLE 2. MEAN AIR POLLUTANT CONCENTRATIONS OVER THE STUDY PERIOD BY FIXED-SITE MONITORING STATION. MEXICO CITY, 1996–1999

Area	Station	O_3* (*ppb*) Mean (SD)	PM_{10} ($\mu g/m^3$) Mean (SD)	NO_2 (*ppb*) Mean (SD)
NW	Tlalnepantla	68.0 (26.7)	66.7 (35.6)	33.7 (15.3)
NE	San Agustín	60.7 (25.8)	†	27.2 (10.9)
NE	Xalostoc	59.7 (25.0)	96.7 (49.4)	28.3 (11.6)
CE	Lagunilla	75.1 (30.1)	†	36.9 (14.0)
CE	Merced	65.7 (28.6)	79.3 (40.8)	34.3 (16.3)
CE	Hangares	69.1 (25.0)	†	35.9 (16.4)
SW	Pedregal	90.0 (33.6)	53.4 (31.9)	31.0 (12.4)
SW	Plateros	79.2 (33.1)	†	29.7 (16.3)
SE	Cerro de la Estrella	66.7 (25.0)	69.6 (35.3)	33.9 (12.5)
SE	Taxqueña	66.8 (24.7)	†	42.6 (13.2)

Definitions of abbreviations: CE = central; NE = northeast; NW = northwest; PM_{10} = particulate matter less than 10 μm in diameter; SE = southeast; SW = southwest.

* 8-hour mean (10 A.M. to 6 P.M.).

† No PM_{10} monitor.

Air Pollution Monitoring

We obtained measurements of NO_2, SO_2, particulate matter with a mass median diameter of less than 10 μm (PM_{10}), ambient O_3 and weather variables (relative humidity and minimum, maximum, and daily average temperature) from 10 government air monitoring stations. We calculated 8-hour means (between 10 A.M. and 6 P.M.) for O_3 and 24-hour means for PM_{10} and NO_2 for each day for which hourly data were available for more than 75% of the time. The selected schools were located within 2 km of 10 fixed-site monitoring stations. Children's exposure assessment was based on data from the station closest to their school. Five monitoring stations (Plateros, Hangares, Taxqueña, Lagunilla, and San Agustín) were not equipped with a TEOM and therefore could not be used to assign PM_{10} exposure. The PM_{10} exposure of children attending the schools concerned was based on data from

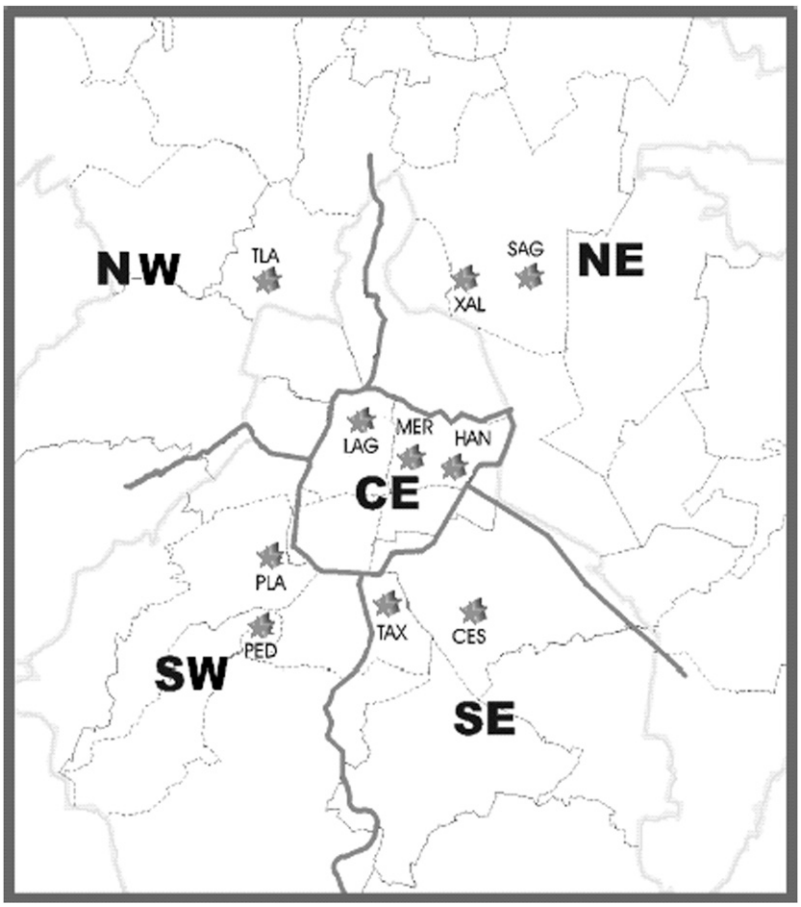

Figure 1. Air monitoring stations in Mexico City. CE = central; CES = Cerro de la Estrella; HAN = Hangares; LAG = Lagunilla; MER = Merced; NE = northeast; NW = northwest; PED = Pedregal; PLA = Plateros; SAG = San Agustín; SE = southeast; SW = southwest; TAX = Taxqueña; TLA, Tlalnepantla; XAL = Xalostoc.

TABLE 3. MEAN AND 10TH, 25TH, 50TH, 75TH, AND 90TH PERCENTILES AND INTERQUARTILE RANGE AIR POLLUTANT 6-MONTH MEAN CONCENTRATIONS OVER THE STUDY PERIOD, MEXICO CITY, 1996–1999

		Percentiles					
	Mean	10th	25th	50th	75th	90th	IQR
O_3, ppb	69.8	54.5	64.3	69.3	75.6	85.4	11.3
PM_{10}, μg/m³	75.6	46.5	55.8	67.5	92.2	112.7	36.4
NO_2, ppb	33.8	22.0	28.9	34.4	40.8	44.5	12.0

Definitions of abbreviations: IQR = interquartile range; NO_2 = nitrogen dioxide; O_3 =ozone; PM_{10} = particulate matter less than 10 μm in diameter.

the nearest station measuring PM_{10} (Pedregal, Merced, Cerro de la Estrella, Merced, and Tlalnepantla). The maximum distance between these schools and the PM_{10} monitoring stations was 6 km.

Long-term exposure for each day of the study period was estimated as the averages over the previous 6 months of the daily O_3 8-hour mean, PM_{10} 24-hour means, and NO_2 24-hour means averaged over the previous 6 months. These averages vary depending on the station assigned to each school. Only low concentrations of So_2 and CO were registered, so their effects were not analyzed.

Statistical Analysis

General linear mixed models were used to evaluate the association between air pollutant concentrations and deficits in lung function growth over time. The outcome variables were the spirometric parameters FVC; FEV_1; forced expiratory flow, midexpiratory phase ($FEF_{25–75\%}$); and FEV_1/FVC from a total of 14,545 test results for 3,170 children. A three-level model was used to distinguish the sources of variation in the response: a first level to identify the variation between phases within children nested within monitoring stations, a second level to identify the variation between subjects within monitoring stations, and a third level to identify the variation between monitoring station variables. We fitted sex-specific models because of the presence of a statistically significant interaction term between time (study phase) and sex ($p < 0.001$). Annual lung function growth was defined as the slope obtained from mixed models given by the coefficient of the interaction term of time with air pollutant concentrations, specifying the variance-covariance matrix as unstructured with random intercept and slope. Our final model included the following variables (based on Akaike's information criteria from the model): time since first test; O_3 averaged over 6 months (O_3-6); previous-day O_3; PM_{10} averaged over 6 months (PM_{10}-6); previous-day PM_{10}; NO_2

TABLE 4. EFFECT OF AMBIENT AIR POLLUTANTS PER YEAR ON LUNG FUNCTION GROWTH IN BOYS AND GIRLS, MEXICO CITY, 1996–1999

Models*	FVC (*ml*) Coefficient (*95% CI*)	FEV_1 (*ml*) Coefficient (*95% CI*)	$FEF_{25–75}$ (*ml/s*) Coefficient (*95% CI*)	FEV_1/FVC (%) Coefficient (*95% CI*)
Girls				
One-pollutant model				
O_3†	−35 (−41 to −29)‡	−24 (−30 to −19)‡	−20 (−32 to −8)§	0.29 (0.17–0.40)‡
PM_{10}‖	−39 (−47 to −31)‡	−29 (−36 to −21)‡	−17 (−36 to 1)	0.12 (0.07–0.17)‡
NO_2¶	−48 (−55 to −41)‡	−32 (−39 to −26)‡	8 (−9 to 21)	0.43 (0.29– 0.57)‡
Two-pollutant models				
O_3†	−25 (−32 to −19)‡	−17 (−23 to −12)‡	−18 (−30 to −6)§	0.21 (0.11–0.32)‡
PM_{10}‖	−30 (−39 to −22)‡	−24 (−31 to −16)‡	−9 (−26 to 9)	0.10 (0.06–0.15)‡
O_3†	−22 (−29 to −16)‡	−16 (−22 to −10)‡	−19 (−31 to −8)§	0.22 (0.09–0.34)§
NO_2¶	−45 (−53 to −37)‡	−33 (−40 to −26)‡	−7 (−23 to 10)	0.29 (0.14–0.43)‡
PM_{10}‖	−21 (−30 to −13)‡	−17 (−25 to −8)‡	−23 (−43 to −4)**	0.07 (0.02–0.13)**
NO_2¶	−41 (−49 to −33)‡	−27 (−34 to −20)‡	14 (−3 to 31)	0.36 (0.22–0.50)‡
Multipollutant model				
O_3†	−19 (−25 to −12)‡	−12 (−18 to −6)‡	−18 (−30 to −5)**	0.18 (0.07 to 0.29)§
PM_{10}‖	−14 (−23 to −5)§	−11 (−20 to −3)§	−7 (−27 to 12)	0.08 (0.03–0.13)§
NO_2¶	−40 (−48 to −32)‡	−30 (−37 to −22)‡	−3 (−21 to 15)	0.21 (0.06–0.35)**
Boys				
One-pollutant model				
O_3†	−25 (−31 to −19)‡	−16 (−21 to −11)‡	−8 (−19 to 4)	0.26 (0.16–0.37)‡
PM_{10}‖	−33 (−41 to −25)‡	−27 (−34 to −19)‡	−18 (−34 to −2)**	0.04 (−0.01 to 0.09)
NO_2¶	−45 (−53 to −37)‡	−26 (−33 to −19)‡	3 (−12 to 19)	0.41 (0.27–0.54)‡
Two-pollutant models				
O_3†	−18 (–24 to –11)‡	−11 (−16 to −5)‡	−6 (−18 to 5)	0.24 (0.13–0.34)‡
PM_{10}‖	−28 (−36 to −19)‡	−22 (−30 to −15)‡	−10 (−27 to 7)	0.04 (−0.01 to 0.09)
O_3†	−13 (−20 to −7)‡	−8 (−14 to −2)‡	−6 (−18 to 5)	0.22 (0.09–0.34)§
NO_2¶	−44 (−53 to −36)‡	−30 (−37 to −23)‡	−13 (−30 to 3)	0.29 (0.14–0.43)‡
PM_{10}‖	−16 (−26 to −7)§	−19 (−27 to −10)‡	−26 (−44 to −9)§	0.005 (−0.06 to 0.05)
NO_2¶	−41 (−49 to −32)‡	−21 (−28 to −13)‡	13 (−3 to 29)	0.43 (0.28–0.57)‡
Multipollutant model				
O_3†	−9 (−16 to −2)‡	−4 (−10 to 2)	−4 (−16 to 8)	0.21 (0.08–0.33)§
PM_{10}‖	−12 (−22 to −3)**	−15 (−23 to −6)§	−12 (−30 to 6)	−0.002 (−0.06 to 0.05)
NO_2¶	−41 (−50 to −32)‡	−25 (−33 to −18)‡	−8 (−25 to 9)	0.26 (0.10–0.41)§

Definition of abbreviations: CI = confidence interval; $FEF_{25–75\%}$, forced expiratory flow, midexpiratory phase; NO_2 = nitrogen dioxide; O_3 = ozone; PM_{10} = particulate matter less than 10 μm in diameter.

* Mixed models adjusted for age, body mass index, height, height by age, weekday time spent in outdoor activities, environmental tobacco smoke exposure, previous-day mean air pollutant concentration, and time since first test (study phase).

† Change in lung function growth in milliliters per interquartile range (IQR) (11.3 ppb) increase in 6-month mean pollutant concentration.

‡ $p < 0.0001$.

§ $p < 0.005$.

‖ Change in lung function growth in ml/IQR (36.4 μg/m³) increase in 6-month mean pollutant concentration.

¶ Change in lung function growth in ml/ IQR (12.0 ppb) increase in 6-month mean pollutant concentration.

** $p < 0.05$.

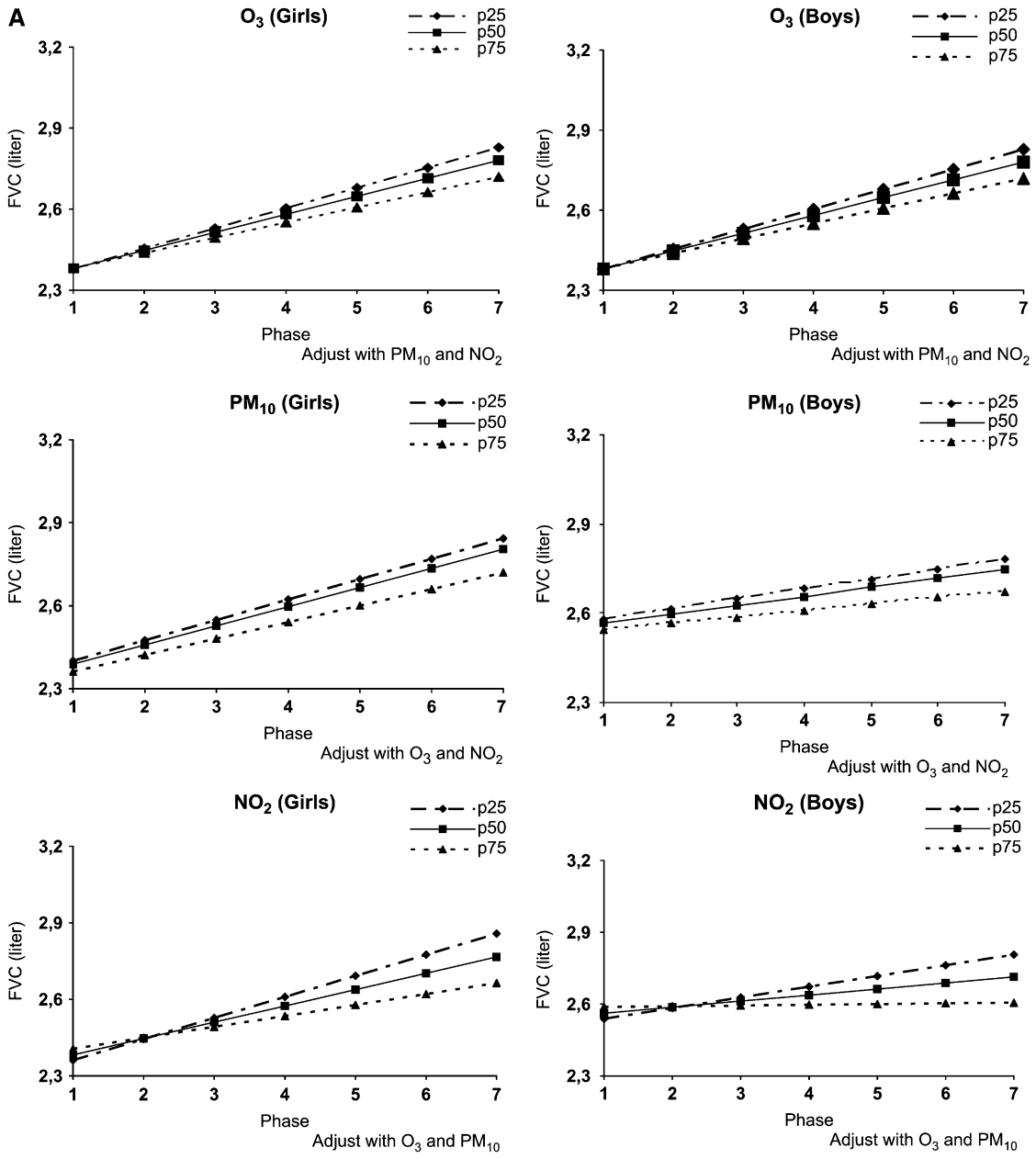

Figure 2. Estimated annual growth in (*A*) FVC; (*B*) FEV_1; (*C*) forced expiratory flow, midexpiratory phase ($FEF_{25-75\%}$) of long-term ozone; particulate matter less than 10 μm in diameter (PM_{10}), and nitrogen dioxide (NO_2) in girls and boys. Mexico City, 1996–1999 (multipollutant models). Adjusted for age, body mass index, height, height by age, weekday time spent in outdoor activities, environmental tobacco smoke exposure, previous-day mean air pollutant concentration, and study phase. Percentiles 25, 50, 75 of ozone (O_3), PM_{10}, and NO_2 correspond to 6-month mean concentrations of 64.3, 69.3, and 75.7 ppb; 56.42, 67.63, and 92.22 μg/m^3; and 28.92, 34.57, and 40.85 ppb, respectively.

averaged over 6 months (NO_2-6); previous-day NO_2; interaction terms of study phase with O_3-6, PM_{10}-6, and NO_2-6; age; body mass index; height; height by age; weekday time spent in outdoor activities; and environmental tobacco smoke. Longitudinal analysis was performed using the PROC MIXED procedure of SAS 8.2 (SAS Institute, Inc., Cary, NC) (for further details of methods used, *see* the online supplement).

RESULTS

Table 1 and Table E1 in the online supplement present the characteristics of the study population (n = 3,170) by study phase and sex. Anthropometric measurements and lung function variables increased over time for both sexes. Figure 1 presents the location of the monitoring stations used in the study. Air pollutant concentrations over the 3-year study period were higher in spring than in fall (Table E2). Over the study period, 8-hour mean O_3 concentrations ranged from 60 ppb (SD, 25) in the northeast area to 90 ppb (SD, 34) in the southwest, and 24-hour mean PM_{10} concentrations ranged from 53 μg/m^3 (SD, 32) in the southwest to 97 μg/m^3 (SD, 49) in the northeast (Table 2). O_3 was negatively associated with PM_{10} ($r = -0.23$; $p < 0.001$) and positively associated with NO_2 ($r = 0.166$; $p < 0.001$).

Table 3 presents O_3, PM_{10}, and NO_2 means and percentiles of 6-month mean concentrations and interquartile range (IQR) during the study period. The widest IQR was observed in 6-month mean PM_{10} concentrations.

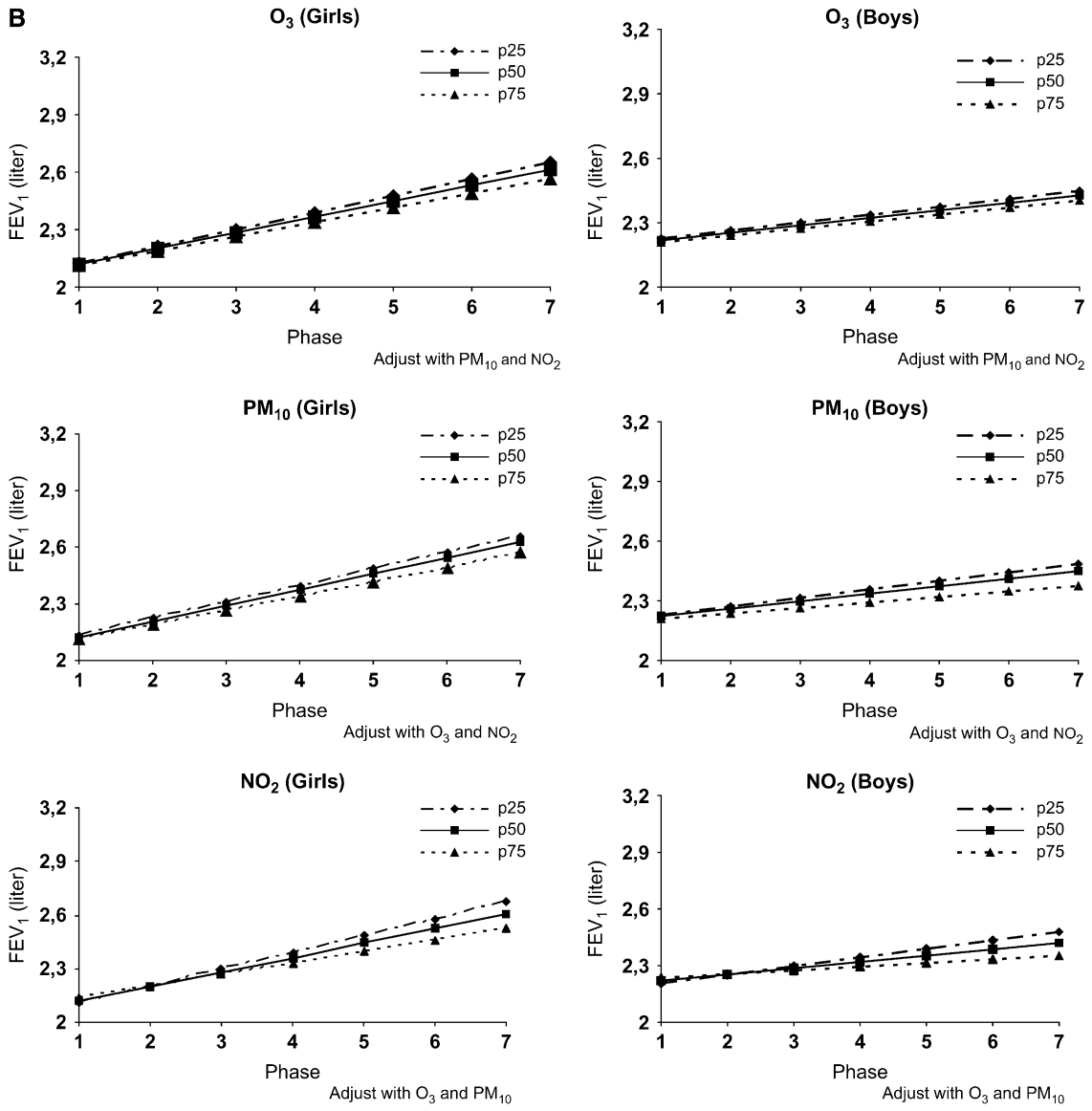

Figure 2. (*Continued*).

Table 4 presents the results by sex of our final mixed models for FVC, FEV_1, and $FEF_{25–75\%}$ adjusted for age, body mass index, height, height by age, weekday time spent in outdoor activities, environmental tobacco smoke exposure, previous-day mean air pollutant concentration, and time since first test. One-pollutant models showed an association between ambient air pollutants and deficits in lung growth. In girls, a 11.3-ppb increase (IQR) in O_3 was associated with an annual deficit of –35 ml (95% confidence interval [CI], –41 to –29) in FVC, −24 ml (95% CI, −30 to −19) in FEV_1, and −20 ml/s (95% CI, −32 to −8) in $FEF_{25–75\%}$. The annual deficits for boys were −25 ml (95% CI, −31 to −19) in FVC, −16 ml (95% CI, −21 to −11) in FEV_1, and −8 ml/s (95% CI, −19 to 4) in $FEF_{25–75\%}$. Ambient PM_{10} and NO_2 concentrations were similarly negatively associated with lung growth. In girls, a 36.4 $\mu g/m^3$ increase (IQR) in PM_{10} was associated with an annual deficit of −39 ml (95% CI, −47 to −31) in FVC and −29 ml (95% CI, −36 to −21) in FEV_1. The corresponding deficits for boys were −33 ml (95% CI, −41 to −25) in FVC and −27 ml (95% CI, −34 to −19) in FEV_1. Slightly larger coefficients were observed for the effect of NO_2. For a 12.0-ppb increase (IQR) in NO_2, the annual deficits were −48 ml (95% CI, −55 to −41) for FVC and −32 ml (95% CI, −39 to −26) for FEV_1 in girls and −45 ml (95% CI, −53 to −37) for FVC and −26 ml (95% CI −33 to −19) for FEV_1 in boys. No significant effect of PM_{10} and NO_2 was observed on $FEF_{25–75\%}$. Estimates from two-pollutant models were not substantially different. In multipollutant models, the negative association of O_3, PM_{10}, and NO_2 with lung function growth persisted, but the effect was slightly stronger for O_3 in girls than boys. Because the observed impact was greater on FVC than on FEV_1, the FEV_1/FVC ratio for both sexes tended to increase with higher pollutant concentrations in all models (Table 4). When the percentage annual changes in predicted values were calculated on the basis of the reference equations for Mexican children (21), the results were similar (Table E4).

Figure 2 presents the estimated growth in FVC (Figure 2A), FEV_1 (Figure 2B), and $FEF_{25–75\%}$ (Figure 2C) for the 25, 50, and 75 percentiles of O_3, PM_{10}, and NO_2 concentrations by sex, obtained from multipollutant models. At the beginning of the study and at each phase of follow-up, children exposed to lower

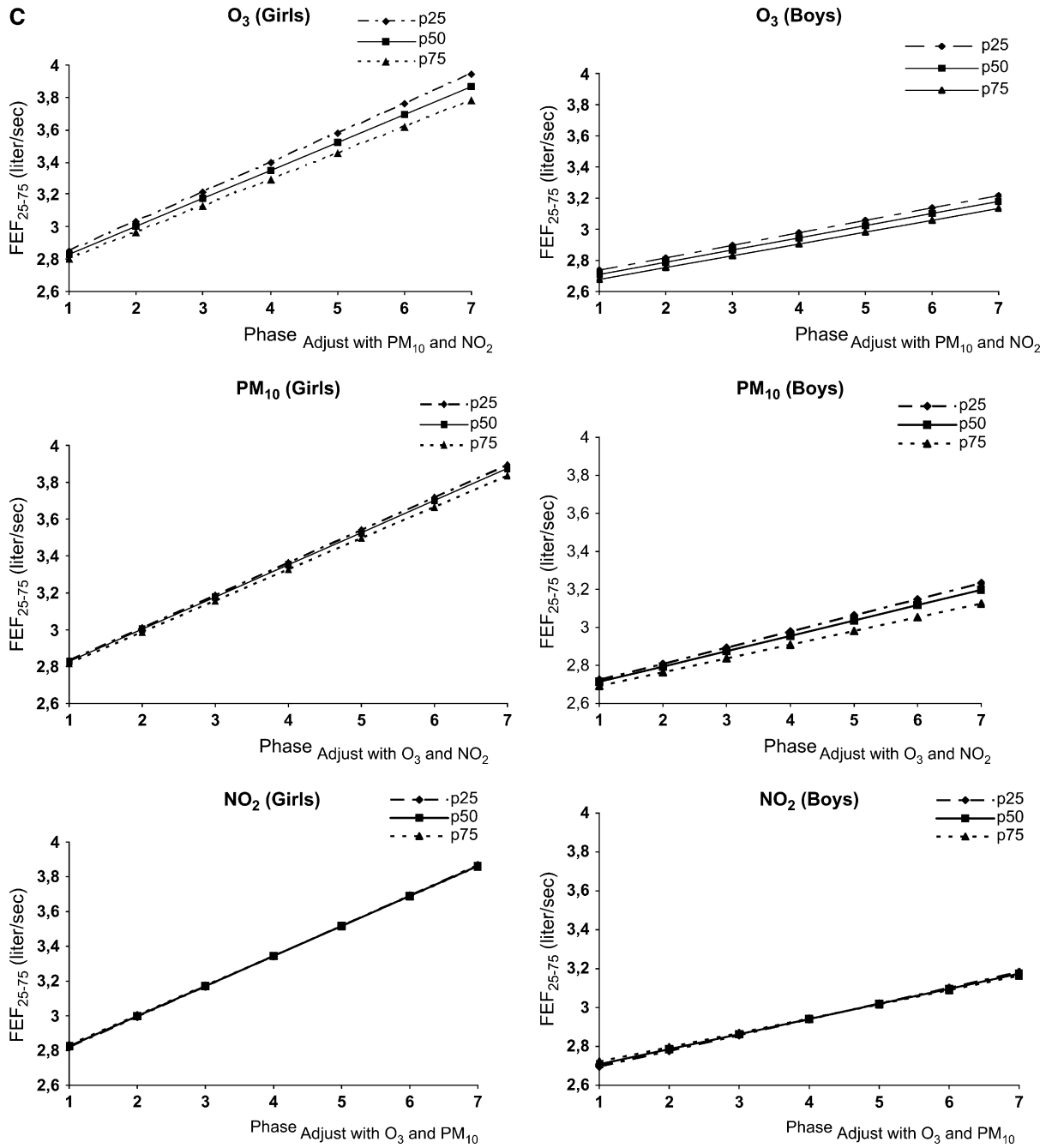

Figure 2. (*Continued*).

O_3 and PM_{10} concentrations had better lung function values than children exposed to higher concentrations.

Because $FEF_{25–75\%}$/FVC is a marker of low volume in small airways and because this might modify the effect of O_3 on $FEF_{25–75\%}$, we stratified by tertiles of $FEF_{25–75\%}$/FVC. O_3 was significantly related to a deficit in lung growth (−5.1% per 10 ppb; 95% CI −8.7 to −1.5) among girls with the lowest $FEF_{25–75\%}$/FVC (lower two tertiles). No effect was observed among girls in the highest tertile or among boys.

DISCUSSION

Our study revealed significant deficits in lung function growth in children with long-term exposure to air pollutants. In one-pollutant models, O_3, PM_{10}, and NO_2 were associated with a significant deficit in FVC and FEV_1 growth in girls and boys. The FEV_1/FVC ratio increased because exposure had a greater impact on FVC than on FEV_1. An association between O_3 and a deficit in $FEF_{25–75\%}$ growth was observed only among girls with a low $FEF_{25–75\%}$/FVC ratio. The effect on FEV_1 during the 3 years of follow-up was slightly greater than that reported for exposure to maternal smoking among children in the United States (22, 23).

A deficit in FVC and FEV_1 growth was observed for O_3, PM_{10}, and NO_2 after adjusting for the acute effect of these pollutants (previous-day concentrations) and for confounding factors. In multipollutant models, O_3 and NO_2 had the strongest effect among girls. These results are in part consistent with previous

results from the CHS, which revealed a deficit in growth mostly with exposure to $PM_{2.5}$, NO_2, and inorganic acid vapor (7, 9, 15). In the CHS, O_3 exposure was associated with a growth deficit in peak expiratory flow rate in fourth graders followed for only 4 of the 8 years of follow-up (8, 22). Lower lung functions in children exposed to higher O_3 concentrations have been reported in cross-sectional studies (24), including one based on CHS data that observed lower peak expiratory flow rate and maximal midexpiratory flow particularly in girls spending more time outdoors (25) and in retrospective (11) and prospective (6) cohort studies. Deficit in lung growth was associated with a set of pollutants including O_3, PM_{10}, and NO_2. Their main source, particularly that of NO_2 and O_3, is traffic related: The former is directly emitted from tailpipes, and the latter is a photochemical reaction to exhaust gases (26). Because the pollutants are correlated, independent effects could not be accurately estimated.

The mechanism of action by which long-term exposure to air pollution produces changes in lung development has not been established. Human and animal studies have demonstrated several changes in lung morphology related to O_3 exposure (27–29), particularly with a predominantly restrictive pattern (30). Calderon and colleagues (16) have suggested that chronic and sustained inhalation of a complex mixture of air pollutants, including O_3 and PM, might be associated with small airway disease. Recently, oxidative stress resulting from increased exposure to oxidant compounds (O_3, NO_2, and particulate components) has been identified as a major feature underlying the toxic effects of air pollutants (31–33). The resulting increased expression of proinflammatory cytokines leads to an enhanced inflammatory response (32) and potential chronic lung damage. It is not clear whether this might result in permanent loss or whether the pattern of exposure (repeated peak exposure versus average exposure) is relevant. Because of the shortness of the 3-year follow-up period and the nonlinear pattern of childhood lung function growth (34), we were unable to estimate the impact on lung function attained in early adulthood.

In our study, exposure to pollutants was associated with a higher FEV_1/FVC ratio, suggesting a restrictive pattern similar to that already described in animals (30) and humans (35). However, the effect of air pollution on the resulting functional pattern has been inconsistent (36, 37), and inflammatory changes in small airways have been observed (11).

Several factors need to be considered when interpreting our results. The exposure values used in studies on the long-term effects of air pollution on lung function growth are usually fixed-site monitoring station data that have been averaged over communities. To reduce exposure misclassification, our study was based on schools located within 2 km of the monitoring stations. In addition, we conducted microenvironmental and personal exposure assessments in a randomly selected subsample of 60 children, using passive O_3 samplers and personal PM_{10} monitors. PM_{10} and O_3 concentrations from personal, indoor, and outdoor monitors were significantly correlated with the measurements obtained from the fixed-site air monitoring stations (38). Our results were not substantially modified when we adjusted our models for potential confounding factors. However, we did not have information on variables such as smoking during pregnancy, birth weight, and atopy, which have been associated with reduced lung function growth (39, 40). Because socioeconomic status might have a differential distribution across monitoring stations and pollution concentrations and might be a determinant of lung function in our population, we tested for interactions between maternal and paternal education levels and air pollutant effects. None of these interactions was significant, suggesting that socioeconomic status could not explain our results.

Lung function testing was conducted by trained technicians, and all spirometry test results were reviewed by a pulmonologist blinded to the location of the school attended by the child. The reproducibility of the tests was good and has been previously reported (20). In the event of missing lung function data, if the data were missing in one phase but not in the next the rate of change could be imputed from the mixed model because the coefficients obtained from the mixed model analysis estimated mean effects.

Conclusions

The results of this 3-year study support the hypothesis that long-term exposure to ambient air pollutants is associated with deficits in lung growth in children. Although we could not identify specific sources, the effect is likely to be due to vehicular exhaust, as observed in the CHS (9). Although it is unclear whether the deficits are permanent, previous studies have reported long-term deficits in lung function associated with air pollutants (9, 11). In addition to the important impact on lung health, early lung function deficits may increase the risk of developing chronic obstructive lung disease later in life as well as increased cardiovascular morbidity and general mortality (41, 42). There is a clear need for stricter air pollution control measures in Mexico City to protect lung growth in children living there.

***Conflict of Interest Statement*:** R.R.-M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. R.P.-P. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. G.O.-F. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. L.M.-A. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. H.M-M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. T.F. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. W.M. received $21,000 from API in 2006 as a contract to develop and publish ozone exposure-response models. D.L. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. I.R. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

***Acknowledgment*:** The authors thank Steve Marshall, Kiros Berhane, James Gauderman, Nino Kuenzli, and Rob McConnell for their important input on this study; the Mexico City monitoring network (RAMA) and the field team for providing high-quality data; and the school principals, teachers, students and parents for their participation. They also thank Garth Evans for reviewing the English manuscript.

References

1. Committee of the Environmental and Occupational Health Assembly of the American Thoracic Society. Health effects of outdoor air pollution. *Am J Respir Crit Care Med* 1996;153:3–50.
2. Schwartz J. Air pollution and children's health. *Pediatrics* 2004;113:1037–1043.
3. Brunekreef B, Holgate ST. Air pollution and health. *Lancet* 2002;360:1233–1242.
4. Künzli N, Lurmann F, Segal M, Ngo L, Balmes J, Tager I. Association between lifetime ambient ozone exposure and pulmonary function in college freshment: Results of a pilot study. *Environ Res* 1997;72:8–23.
5. Galizia A, Kinney P. Long-term residence in areas of high ozone: associations with respiratory health in a nationwide sample of nonsmoking young adults. *Environ Health Perspect* 1999;107:675–679.
6. Frischer T, Studnicka M, Gartner C, Tauber E, Horak F, Veiter A, Spengler J, Kuhr J, Urbanek R. Lung function growth and ambient ozone: a three-year population study in school children. *Am J Respir Crit Care Med* 1999;160:390–396.
7. Gauderman WJ, McConnell R, Gilliland F, London S, Thomas D, Avol E, Vora H, Berhane K, Rappaport EB, Lurmann F, *et al.* Association between air pollution and lung function growth in southern California children. *Am J Respir Crit Care Med* 2000;162:1383–1390.
8. Gauderman WJ, Gilliland F, Vora H, Avol E, Stram D, McConnell R, Thomas D, Lurmann F, Margolis HG, Rappaport EB, *et al.* Association between air pollution and lung function growth in southern California children: results from a second cohort. *Am J Respir Crit Care Med* 2002;166:76–84.

9. Gauderman WJ, Avol E, Gilliland F, Vora H, Thomas D, Berhane K, McConnell R, Kuenzli N, Lurmann F, Rappaport EB, *et al.* The effect of air pollution on lung development from 10 to 18 years of age. *N Engl J Med* 2004;351:1057–1067.
10. Kopp M, Bohnet W, Frischer T, Ulmer C, Studnicka M, Ihorst G, Gardner C, Forster J, Urbanek R, Kuehr J. Effects of ambient ozone on lung function in children over a two-summer period. *Eur Respir J* 2000;16: 893–900.
11. Tager IB, Balmes J, Lurmann F, Ngo L, Alcorn S, Kunzli N. Chronic exposure to ambient ozone and lung function in young adults. *Epidemiology* 2005;16:751–759.
12. Offical Mexican Norm. Environmental health: criteria for the evaluation of ambient air quality, with respect to ozone (O3) in ambient air, as a protective measure for the health of the population. Mexico City: Mexican Health Ministry: 1993.
13. Romieu I, Meneses F, Ruiz S, Huerta J, Sienra JJ, White M, Etzel R, Hernandez-Avila M. Effects of intermittent ozone exposure on peak expiratory flow and respiratory symptoms among asthmatic children in Mexico City. *Arch Environ Health* 1997;52:368–376.
14. Romieu I, Meneses F, Ruiz S, Sienra-Monge JJ, Huerta J, White MC, Etzel RA. Effects of air pollution on the respiratory health of asthmatic children living in Mexico City. *Am J Respir Crit Care Med* 1996;154: 300–307.
15. Castillejos M, Gold DR, Dockery D, Tosteson T, Baum T, Speizer FE. Effects of ambient ozone on respiratory function and symptoms in Mexico City schoolchildren. *Am Rev Respir Dis* 1992;145:276–282.
16. Calderón-Garcidueñas L, Mora-Tiscareño A, Chung CJ, Valencia G, Fordham LA, García R, Osnaya N, Romero L, Acuña H, Villarreal-Calderón A. Exposure to air pollution is associated with lung hyperinflation in health children and adolescents in Southwest Mexico City: a pilot study. *Inhal Toxicol* 2000;12:537–561.
17. Rojas R, Romieu I, Perez-Padilla R, Mendoza L, Fortoul TI, Olaiz G. Lung growth and chronic exposure to air pollutant in children residing in Mexico City. *Am J Respir Crit Care Med* 2004;168:A20.
18. Rojas M, Romieu I, Perez-Padilla R, Mendoza L, Fortoul TI, Olaiz G. Lung function growth in children with long-term exposure to ozone in Mexico City. *Am J Respir Crit Care Med* 2005;171:A523.
19. Crapo RO. Pulmonary function testing. In: Baum GL, Celli BR, Crapo JD, Karlinsky JB, editors. Textbook of pulmonary diseases. Philadelphia: Lippincott Williams and Wilkins; 1998;199–218.
20. Perez-Padilla R, Regalado-Pineda J, Mendoza L, Rojas R, Torres V, Borja-Aburto V, Olaiz G. Spirometric variability in a longitudinal study of school-age children. *Chest* 2003;123:1090–1095.
21. Perez-Padilla R, Regalado-Pineda J, Rojas M, Catalan M, Mendoza L, Rojas R, Chapela R, Villalba J, Torres V, Borja-Aburto V, *et al.* Spirometric function in children of Mexico City compared to Mexican-American children. *Pediatr Pulmonol* 2003;35:177–183.
22. Tager IB, Weiss ST, Munoz A, Rosner B, Speizer FE. Longitudinal study of the effects of maternal smoking on pulmonary function in children. *N Engl J Med* 1983;309:699–703.
23. Wang X, Wypij D, Gold DR, Speizer FE, Ware JH, Ferris BG Jr, Dockery DW. A longitudinal study of the effects of parental smoking on pulmonary function in children 6–18 years. *Am J Respir Crit Care Med* 1994; 149:1420–1425.
24. Kinney PL, Thurston GD, Raizenne M. The effects of ambient ozone on lung function in children: a reanalysis of six summer camp studies. *Environ Health Perspect* 1996;104:170–174.
25. Peters JM, Avol E, Gauderman WJ, Linn WS, Navidi W, London SJ, Margolis H, Rappaport E, Vora H, Gong H, *et al.* A study of twelve southern California communities with differing levels and types of air pollution. II. Effects on pulmonary function. *Am J Respir Crit Care Med* 1999;159:768–775.
26. Almanaque de datos y tendencias de la calidad del aire en ciudades mexicanas. Mexico, D.F.: Secretaría de Medio Ambiente y Recursos Naturales, Instituto Nacional de Ecología; 2000.
27. Tyler WS, Tyler NK, Magliano DJ. Effects of ozone inhalation on lungs of juvenile monkeys: morphometry alter a 12-month exposure and following a 6-month post-exposure period. In: Berglund RL, Lawson DR, McKee DJ, editors. Trophospheric ozone and the environment. Pittsburgh, PA: Air and Waste Management Association; 1991. pp. 151–160.
28. Lippman M. Health effects of ozone; a critical review. *J Air Waste Manag Assoc* 1989;39:672–695.
29. Paige RC, Plopper CG. Acute and chronic effects of ozone in animal models. In: Holgate ST, Samet JM, Koren HS, Maynard R, editors. Air pollution and health. London: Academic Press; 1999. pp. 530–557.
30. Costa DL, Tepper JS, Stevens MA, Watkinson WP, Doerfler DL, Gelzleichter TR, Last JA. Restrictive lung disease in rats exposed chronically to an urban profile of ozone. *Am J Respir Crit Care Med* 1995;151:1512–1518.
31. Kelly FJ. Oxidative stress: its role in air pollution and adverse health effects. *Occup Environ Med* 2003;60:612–616.
32. Saxon A, Diaz-Sanchez D. Air pollution and allergy: you are what you breathe. *Nat Immunol* 2005;6:223–226.
33. Cross CE, Valacchi G, Schock B, Wilson M, Weber S, Eiserich J, van der Vliet A. Environmental oxidant pollutant effects on biologic systems: a focus on micronutrient antioxidant-oxidant interactions. *Am J Respir Crit Care Med* 2002;166:S44–S50.
34. Pérez-Padilla R, Regalado J, Rojas M, Catalán M, Mendoza L, Rojas R, Chapela R, Villalba J, Torres V, Borja V, *et al.* Spirometric function in children of Mexico City compared to Mexican-American children. *Pediatr Pulmonol* 2003;35:177–183.
35. Bromberg PA, Koren HS. Ozone-induced human respiratory dysfunction and disease. *Toxicol Lett* 1995;82:307–316.
36. Avol E, Linn W, Shamoo D, Spier C, Valencia LM, Venet TG, Trim SC, Hackney JD. Short-term respiratory effects of photochemical oxidant exposure in exercising children. *JAPCA* 1987;37:158–162.
37. Castillejos M, Gold DR, Damokosh AL, Serrano P, Allen G, Mcdonnell WF, Dockery D, Ruiz-Velasco S, Hernández M, Hayes C. Acute effects of ozone on the pulmonary function of exercising school-children from Mexico City. *Am J Respir Crit Care Med* 1995;152:1501–1507.
38. Torres VM, Olaiz G, Rojas R, Pares P, Pérez-Padilla R. Patrones de exposición a PM10 y Ozono en una cohorte de niños escolares de la ciudad de México. Mexico, D.F.: Conserva; 1999.
39. Bakke PS. Factors affecting growth of FEV1. *Monaldi Arch Chest Dis* 2003;59:103–107.
40. Stick S. The contribution of airway development to paedriatic and adult lung disease. *Thorax* 2000;55:587–594.
41. Schroeder EB, Welch VL, Couper D, Nieto FJ, Liao D, Rosamond WD, Heiss G. Lung function and incident coronary heart disease: the Atherosclerosis Risk in Communities Study. *Am J Epidemiol* 2003;158: 1171–1181.
42. Schunemann HJ, Dorn J, Grant BJ, Winkelstein WJ, Trevisan M. Pulmonary function is a long-term predictor of mortality in the general population: 29-year follow-up of the Buffalo Health Study. *Chest* 2000; 118:656–664.